

Express Mail No.: EV561559066US
International Application No.: PCT/US2003/034655
International Filing Date: October 31, 2003
Preliminary Amendment

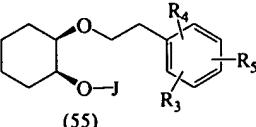
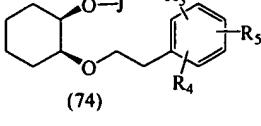
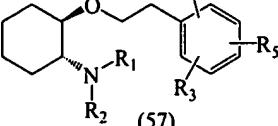
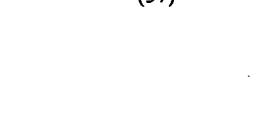
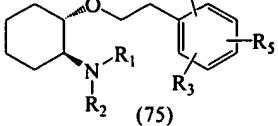
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

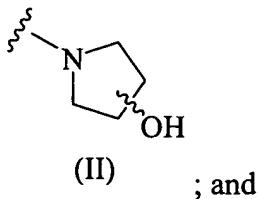
Listing of Claims:

1-100. (Cancelled)

101. (New) A method of stereoselectively making an aminocyclohexyl ether comprising:

reacting a compound of formula (55),

(55) , or a compound
of formula (74),

(74) , with a compound of formula (56),

(56) , to form a compound of formula (57),

(57) , or a compound of formula (75),

(75) , respectively,

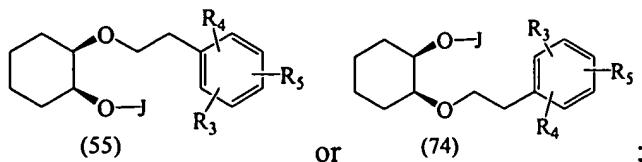
wherein R₁ and R₂, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):



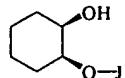
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wherein R_3 , R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1 - C_6 alkoxy, with the proviso that R_3 , R_4 and R_5 cannot all be hydrogen; and wherein O-J is a leaving group.

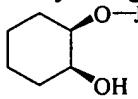
102. (New) A method of making a compound of formula (55) or formula (74):



wherein the method comprises:

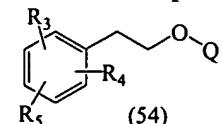


alkylating a compound of formula (53), (53), or a compound of

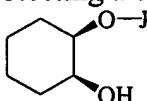


formula (84), (84), with a compound of formula (54), R_5 (54); to form the compound of formula (55) or the compound of formula (74); respectively; and

the compound of formula (55) or the compound of formula (74); respectively; and



optionally protecting a compound of formula (53), (53), or a



compound of formula (84), (84), before said alkylating step;

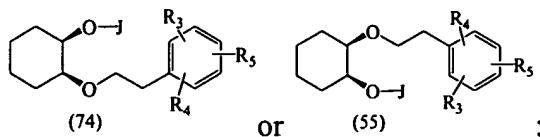
wherein O-Q is a leaving group that reacts with -OH in formula (53) or formula (84) to form the compound of formula (55) or the compound of formula (74), such that the stereochemical configuration of the compound of formula (53) or the compound of formula (84) is retained in the compound of formula (55) or the compound of formula (74), respectively;

wherein R₃, R₄ and R₅ are independently selected from hydrogen, hydroxy, and C₁-C₆alkoxy, with the proviso that R₃, R₄ and R₅ cannot all be hydrogen; and

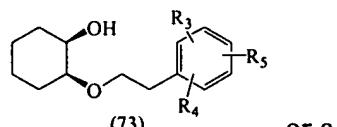
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wherein O-J is a leaving group.

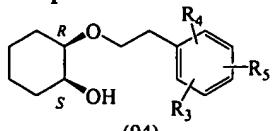
103. (New) A method of making a compound of formula (74) or formula (55):



wherein the method comprises:



activating a compound of formula (73),

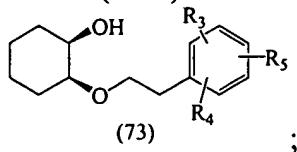


compound of formula (94), ⁽⁹⁴⁾, with a hydroxy activating reagent to form the compound of formula (74) or the compound of formula (55), respectively;

wherein R₃, R₄ and R₅ are independently selected from hydrogen, hydroxy, and C₁-C₆alkoxy, with the proviso that R₃, R₄ and R₅ cannot all be hydrogen; and

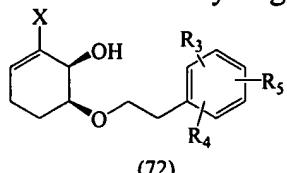
wherein O-J is a leaving group.

104. (New) A method of making a compound of formula (73):



wherein the method comprises:

hydrogenating and hydrogenolyzing a compound of formula (72),



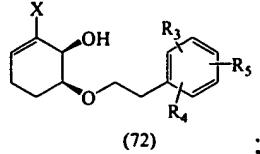
(72) , to form the compound of formula (73);

wherein X is a halide; and

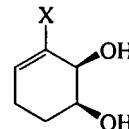
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wherein R_3 , R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1 - C_6 alkoxy, with the proviso that R_3 , R_4 and R_5 cannot all be hydrogen.

105. (New) A method of making a compound of formula (72):



wherein the method comprises:



alkylating a compound of formula (51), (51), with a compound of

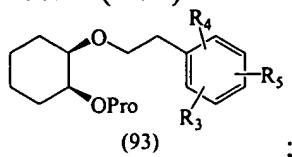
formula (54), (54), to form the compound of formula (72);

wherein X is a halide

wherein R_3 , R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1 - C_6 alkoxy, with the proviso that R_3 , R_4 and R_5 cannot all be hydrogen; and

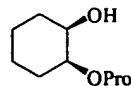
wherein O-Q is a leaving group that reacts with -OH in the compound of formula (51) to form the compound of formula (72), such that the stereochemical configuration of the compound of formula (51) is retained in the compound of formula (72).

106. (New) A method of making a compound of formula (93):



wherein the method comprises:

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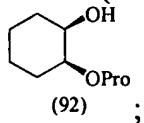
alkylating a compound of formula (92), (92) , with a compound of formula (54), (54) , to form the compound of formula (93);

wherein Pro is a protecting group;

wherein R_3 , R_4 and R_5 are independently selected from hydrogen, hydroxy, and C_1 - C_6 alkoxy, with the proviso that R_3 , R_4 and R_5 cannot all be hydrogen; and

wherein O-Q is a leaving group that reacts with -OH in the compound of formula (92) to form the compound of formula (93), such that the stereochemical configuration of the compound of formula (92) is retained in the compound of formula (93).

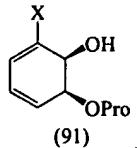
107. (New) A method of making a compound of formula (92):



;

wherein the method comprises:

hydrogenating and hydrogenolyzing a compound of formula (91),

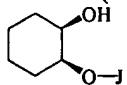


(91) , to form the compound of formula (92);

wherein Pro is a protecting group; and

wherein X is a halide.

108. (New) A method of making a compound of formula (53):

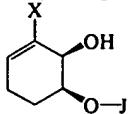


(53) ;

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wherein the method comprises:

hydrogenating and hydrogenolyzing a compound of

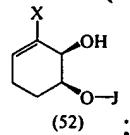


formula (52), (52), to form the compound of formula (53);

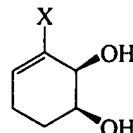
wherein X is a halide; and

wherein O-J is a leaving group.

109. (New) A method of making a compound of formula (52):



wherein the method comprises:



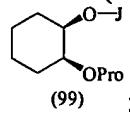
activating a compound of formula (51), (51), with a hydroxy

activating reagent to form the compound of formula (52);

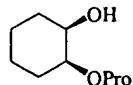
wherein X is a halide; and

wherein O-J is a leaving group.

110. (New) A method of making a compound of formula (99):



wherein the method comprises:



activating a compound of formula (92), (92), with a hydroxy

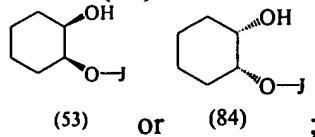
activating reagent to form the compound of formula (99);

wherein Pro is a protecting group; and

wherein O-J is a leaving group.

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111. (New) A method of making a compound of formula (53) or a compound of formula (84):



wherein the method comprises:

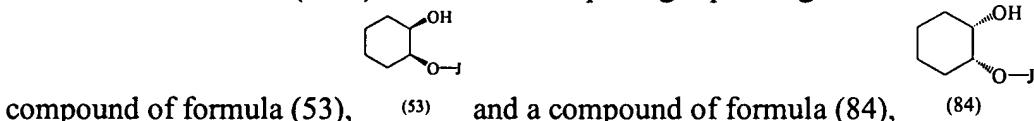
removing a functional group G or G₁ from a compound of formula (85),



(85) , or a compound of formula (86), (86) , respectively, to form the compound of formula (53) or the compound of formula (84), respectively;

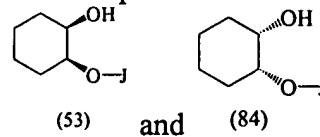
wherein O-J is a leaving group.

112. (New) A method comprising separating a racemic mixture of a

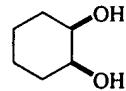


compound of formula (53), (53) and a compound of formula (84), (84) .

113. (New) A method of forming a racemic mixture of a compound of formula (53) and a compound of formula (84):



wherein the method comprises:



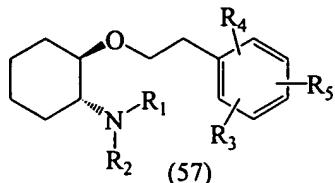
activating a compound of formula (83), (83) , with a hydroxy

activating reagent to form the racemic mixture of the compound of formula (53) and the compound of formula (84);

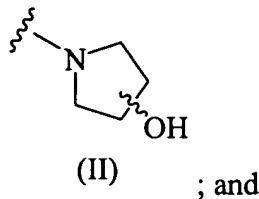
wherein O-J is a leaving group.

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114. (New) A method for stereoselectively making an aminocyclohexyl ether of formula (57):

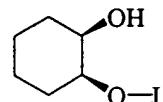


wherein R₁ and R₂, when taken together with the nitrogen atom to which they are directly attached in formula (57), form a ring denoted by formula (II):

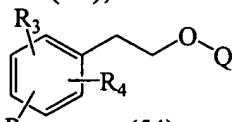


wherein R₃, R₄ and R₅ are independently selected from hydrogen, hydroxy and C₁-C₆alkoxy, with the proviso that R₃, R₄ and R₅ cannot all be hydrogen;

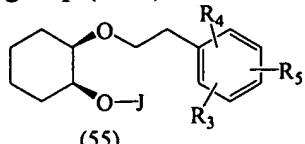
wherein the method comprises:



(a) reacting a compound of formula (53), (53) , wherein O-J is



a leaving group, with a compound of formula (54), (54) , wherein R₃, R₄ and R₅ are as defined above and O-Q is a leaving group that reacts with the hydroxy group (-OH) in formula (53) to form a compound of formula (55),



, such that the stereochemical configuration of the compound of formula (53) is retained in the compound of formula (55);

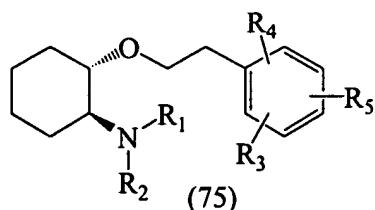
(b) optionally protecting the compound of formula (53) before the first reaction; and

(c) reacting the compound of formula (55) with a compound of

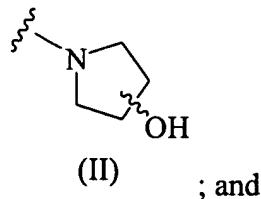


formula (56), (56), wherein R₁ and R₂ are as defined above, to form the aminocyclohexyl ether of formula (57).

115. (New) A method for stereoselectively making an aminocyclohexyl ether of formula (75):

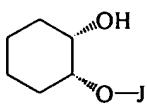


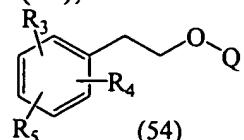
wherein R₁ and R₂, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):

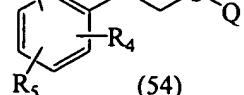


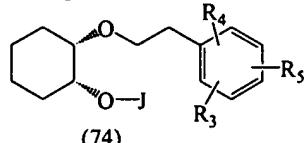
wherein R₃, R₄ and R₅ are independently selected from hydrogen, hydroxy and C₁-C₆alkoxy, with the proviso that R₃, R₄ and R₅ cannot all be hydrogen; wherein the method comprises:

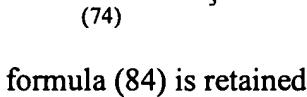
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(a) reacting a compound of formula (84), (84), wherein O-J



is a leaving group, with a compound of formula (54), (54), wherein R3, R4 and R5 are as defined above and O-Q is a leaving group that reacts with the hydroxy group (-OH) in the compound of formula (84) to form a compound of formula (74),



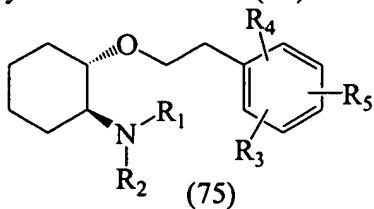
(74), such that the stereochemical configuration of the compound of formula (84) is retained in the compound of formula (74);

(b) optionally protecting the compound of formula (84) before the first reaction step (a); and

(c) reacting the compound of formula (74) with a compound of 

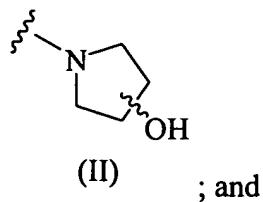
formula (56), (56), wherein R1 and R2 are as defined above, to form the aminocyclohexyl ether of formula (75).

116. (New) A method for stereoselectively making an aminocyclohexyl ether of formula (75):

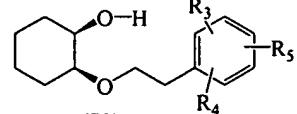
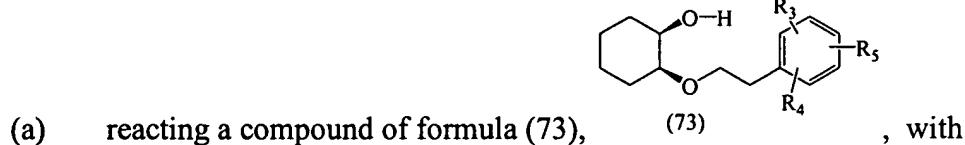


wherein R1 and R2, when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):

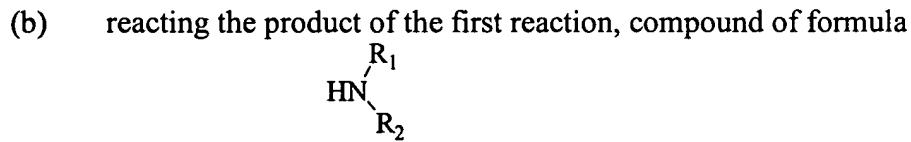
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wherein R_3 , R_4 and R_5 are independently selected from hydrogen, hydroxy and C_1 - C_6 alkoxy, with the proviso that R_3 , R_4 and R_5 cannot all be hydrogen; wherein the method comprises:

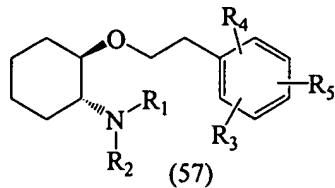


a hydroxy activating reagent to form a compound of formula (74), , wherein $O-J$ is a leaving group, and R_3 , R_4 and R_5 are as defined above; and



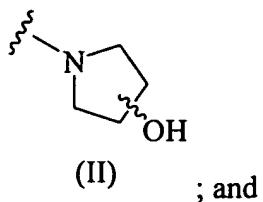
(74) with a compound of formula (56), (56) , wherein R_1 and R_2 are as defined above, to form the aminocyclohexyl ether of formula (75).

117. (New) A method for stereoselectively making an aminocyclohexyl ether of formula (57):



wherein R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (57) or (75), form a ring denoted by formula (II):

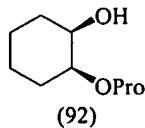
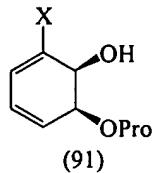
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wherein R₃, R₄ and R₅ are independently selected from hydrogen, hydroxy and C₁-C₆alkoxy, with the proviso that R₃, R₄ and R₅ cannot all be hydrogen;

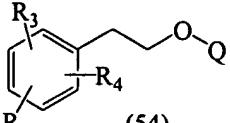
wherein the method comprises:

(a) hydrogenating and hydrogenolyzing a compound of formula (91),

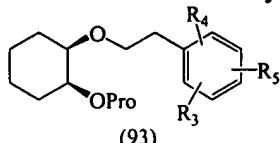


, to form a compound of formula (92), , wherein Pro is a protecting group and X is a halide;

(b) alkylating the compound of formula (92) with a compound of

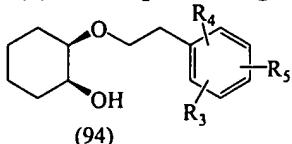


formula (54), R₅ , , wherein R₃, R₄ and R₅ are as defined above and O-Q is a leaving group that reacts with the hydroxy group in formula (92) to form a compound



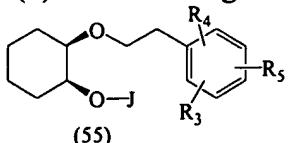
of formula (93), , such that the stereochemical configuration of the compound of formula (92) is retained in the compound of formula (93);

(c) deprotecting the compound of formula (93) to form a compound of



formula (94), ;

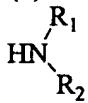
(d) activating the compound of formula (94) to form a compound of



formula (55), , wherein O-J is a leaving group; and

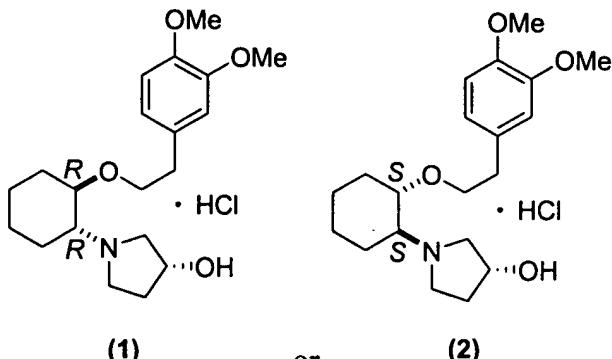
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(e) reacting the compound of formula (55) with a compound of



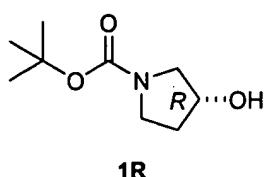
formula (56), (56), wherein R_1 and R_2 are as defined above, to form the aminocyclohexyl ether of formula (57).

118. (New) A method of making compound (1) or compound (2):



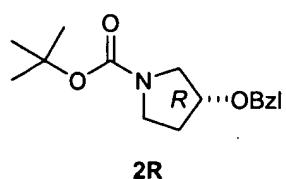
wherein the method comprises:

a) reacting  with $(\text{Boc})_2\text{O}$ under suitable conditions to yield (1R):



b) reacting compound (1R) with benzyl bromide under suitable

conditions to form compound (2R):



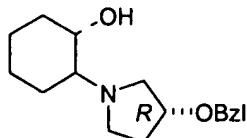
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c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):

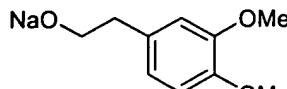


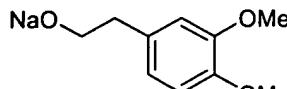
3R ;

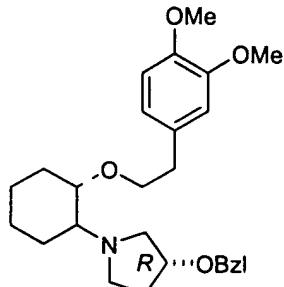
d) reacting compound (3R) with  under suitable conditions to form compound (4R):



4R ;



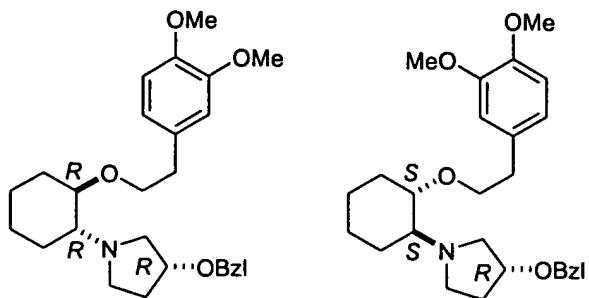
e) reacting compound (4R) with  under suitable conditions to form compound (5R);



5R ;

f) resolving compound (5R) under suitable conditions to form compound (5RRR) and compound (5SSR):

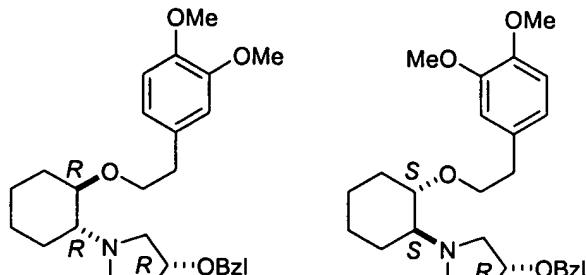
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5RRR and **5SSR** ; and

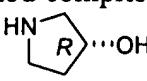
g) hydrogenolyzing compound (5RRR) under suitable conditions to form compound (1), as described above, and hydrogenolyzing compound (5SSR) under suitable conditions to form compound (2), as described above.

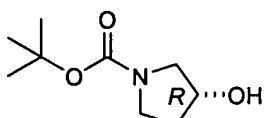
119. (New) A method of making compound (5RRR) or compound (5SSR):



5RRR and **5SSR** ;

wherein the method comprises:

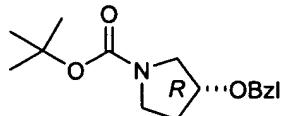
a) reacting  with (Boc)₂O under suitable conditions to form compound (1R):



1R ;

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b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):



2R ;

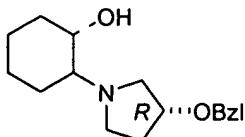
c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):



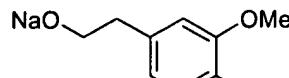
3R ;



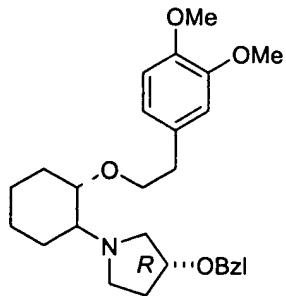
d) reacting compound (3R) with cyclopentylmethyl oxide under suitable conditions to form compound (4R):



4R ;



e) reacting compound (4R) with 4,4'-dimethoxydiphenylmethane under suitable conditions to form compound (5R);

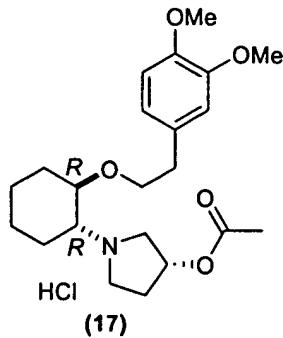


5R ; and

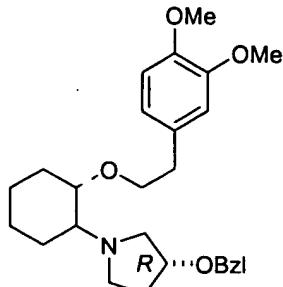
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f) resolving compound (5R) under suitable conditions to form compound (5RRR) and compound (5SSR), as described above.

120. (New) The method of Claim 119 further comprising:
reacting compound (5RRR) under suitable conditions to form compound (17):



121. (New) A method of making compound (5R):

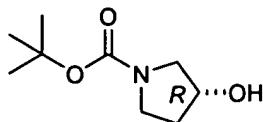


;

wherein the method comprises:

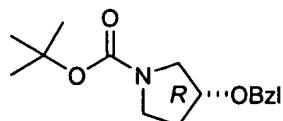
a) reacting with (Boc)₂O under suitable conditions to form compound (1R):

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1R ;

b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):



2R ;

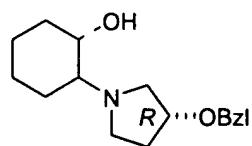
c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):



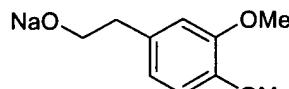
3R ;

d) reacting compound (3R) with

under suitable conditions to form compound (4R):



4R ; and

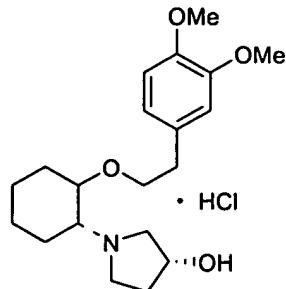


e) reacting compound (4R) with

under suitable conditions to form compound (5R), as described above.

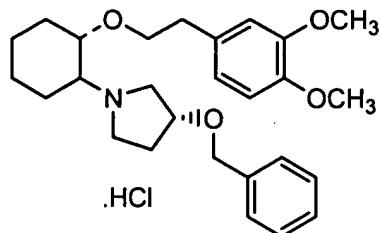
122. (New) The method of Claim 121 further comprising:
reducing compound (5R) under suitable conditions to form compound (4):

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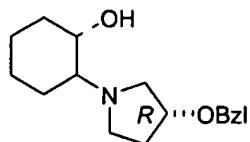


(4)

123. (New) The method of Claim 121 further comprising:
reacting compound (5R) under suitable conditions to form compound (12):



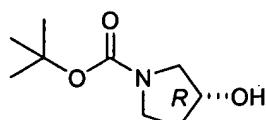
124. (New) A method of making compound (4R):



4R ;

wherein the method comprises:

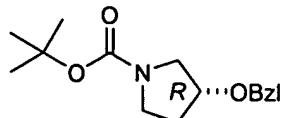
a) reacting
with (Boc)₂O under suitable conditions to
form compound (1R):



1R ;

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b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):



2R ;

c) hydrolyzing compound (2R) under suitable conditions to form compound (3R):



3R ; and



d) reacting compound (3R) with under suitable conditions to form compound (4R), as described above.

125. (New) A method of making compound (3R):

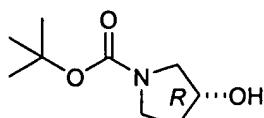


3R ;

wherein the method comprises:

a) reacting

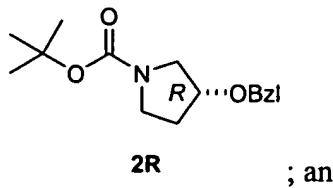
with $(\text{Boc})_2\text{O}$ under suitable conditions to form compound (1R):



1R ;

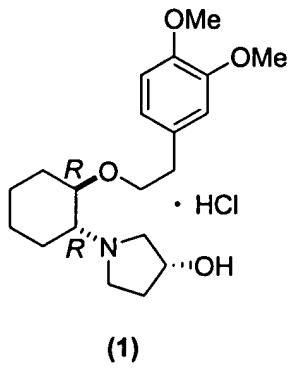
b) reacting compound (1R) with benzyl bromide under suitable conditions to form compound (2R):

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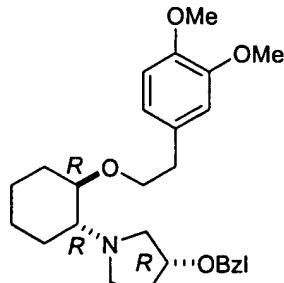


c) hydrolyzing compound (2R) under suitable conditions to form compound (3R), as described above.

126. (New) A method of making compound (1):



wherein the method comprises hydrogenolyzing compound (5RRR):



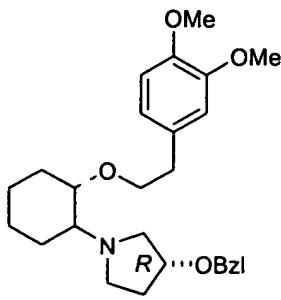
5RRR

under suitable conditions to form compound (1), as described above.

127. (New) The method of claim 126 further comprising, prior to the hydrogenolyzing step,

resolving compound (5R):

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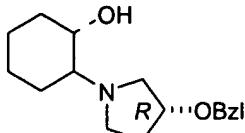


5R

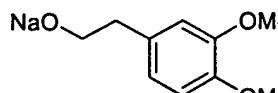
under suitable conditions to form compound (5RRR), as described above.

128. (New) The method of claim 127 further comprising, prior to the resolving step,

reacting compound (4R):

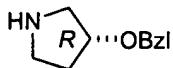


4R

with  under suitable conditions to form compound (5R), as described above.

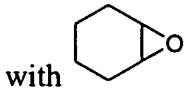
129. (New) The method of claim 128 further comprising, prior to the reacting step,

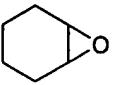
reacting compound (3R):

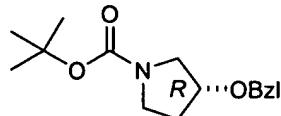


3R

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with  under suitable conditions to form compound (4R), as described above.

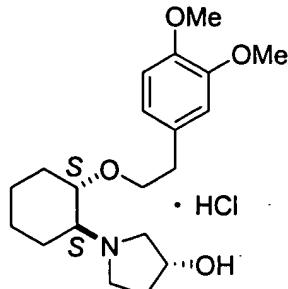
130. (New) The method of claim 129 further comprising, prior to the reaction of compound (3R) with  , hydrolyzing compound (2R):



2R

under suitable conditions to form compound (3R), as described above.

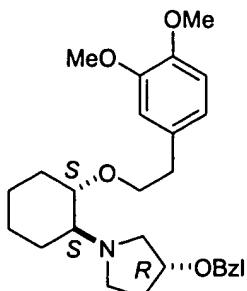
131. (New) A method of making compound (2):



(2)

;

wherein the method comprises hydrogenolyzing compound (5SSR):



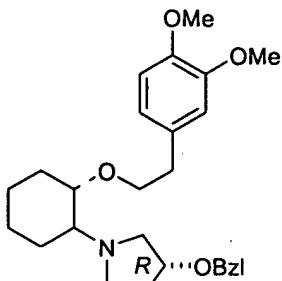
5SSR

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under suitable conditions to form compound (2), as described above.

132. (New) The method of claim 131 further comprising, prior to the hydrogenolyzing step,

resolving compound (5R):

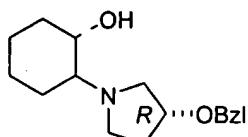


5R

under suitable conditions to form compound (5SSR), as described above.

133. (New) The method of claim 132 further comprising, prior to the resolving step,

reacting compound (4R):



4R

with

under suitable conditions to form compound (5R), as described above.

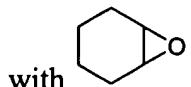
134. (New) The method of claim 133 further comprising, prior to the reacting step,

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reacting compound (3R):



3R

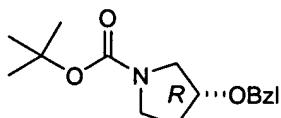


with under suitable conditions to form compound (4R), as described above.

135. (New) The method of claim 134 further comprising, prior to the



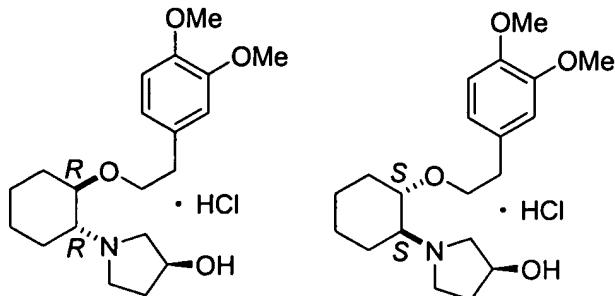
reaction of compound (3R) with , hydrolyzing compound (2R):



2R

under suitable conditions to form compound (3R), as described above.

136. (New) A method of making compound (6) or compound (7):



(6)

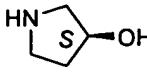
or

(7)

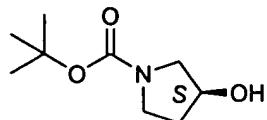
;

wherein the method comprises:

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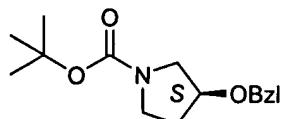
a) reacting  with $(\text{Boc})_2\text{O}$ under suitable conditions to

form the following compound:



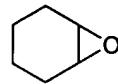
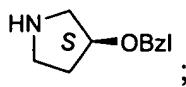
;

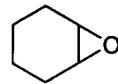
b) reacting the compound formed in step a) with benzyl bromide under suitable conditions to form the following compound:

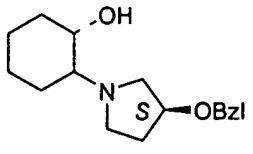


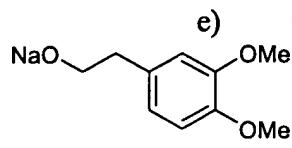
;

c) hydrolyzing the compound formed in step b) under suitable conditions to form the following compound:

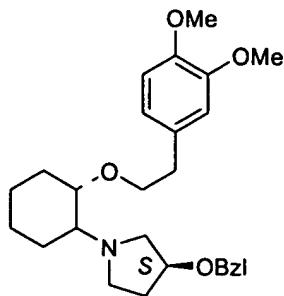


d) reacting the compound formed in step c) with  under suitable conditions to form the following compound:



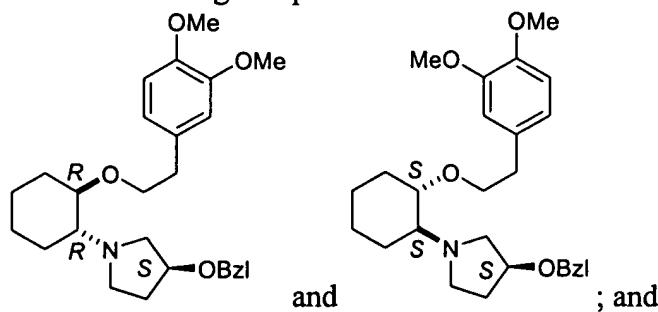
e) reacting the compound formed in step d) with  under suitable conditions to form the following compound:

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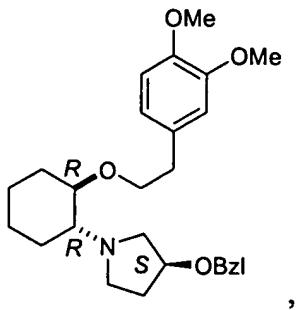


;

f) resolving the compound formed in step e) under suitable conditions to form the following compounds:

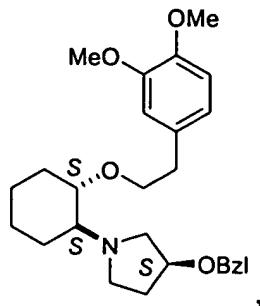


g) hydrogenolyzing the following compound formed in step f):



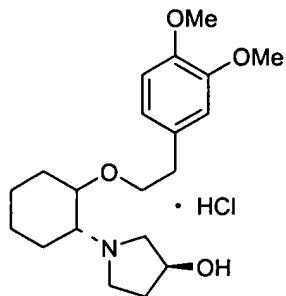
under suitable conditions to form compound (6), as described above;
and hydrogenolyzing the following compound formed in step f):

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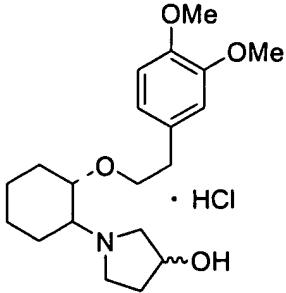
under suitable conditions to form compound (7), as described above.

137. (New) The method of claim 136 further comprising:
reducing the compound formed in step e) under suitable conditions to
form compound (5):



(5)

138. (New) A method of making compound (3):

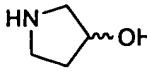


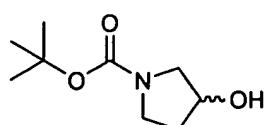
(3)

;

wherein the method comprises:

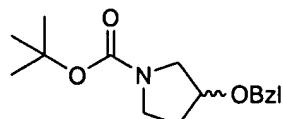
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a) reacting  with $(\text{Boc})_2\text{O}$ under suitable conditions to form the following compound:



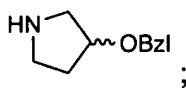
;

b) reacting the compound formed in step a) with benzyl bromide under suitable conditions to form the following compound:

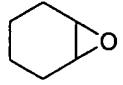


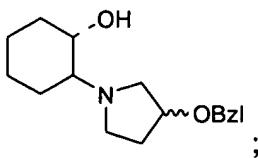
;

c) hydrolyzing the compound formed in step b) under suitable conditions to form the following compound:

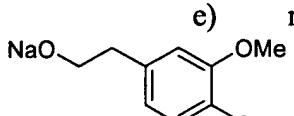


;

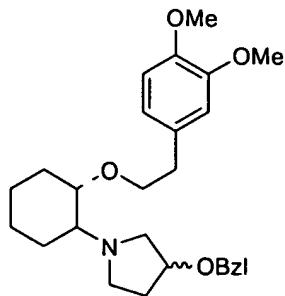
d) reacting the compound formed in step c) with  under suitable conditions to form the following compound:



;

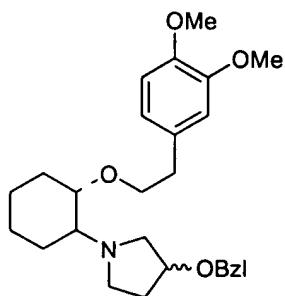
e) reacting the compound formed in step d) with  under suitable conditions to form the following compound:

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;

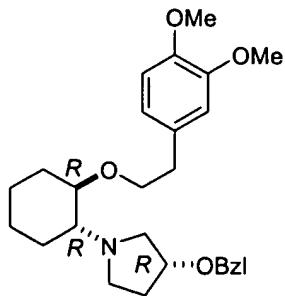
f) hydrogenolyzing the following compound formed in step e):



,

under suitable conditions to form compound (3), as described above.

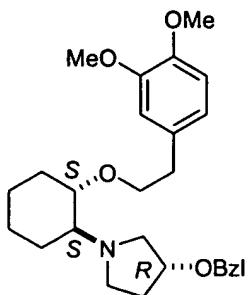
139. (New) The compound (5RRR):



5RRR

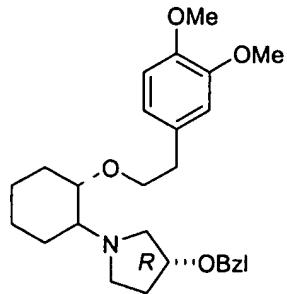
140. (New) The compound (5SSR):

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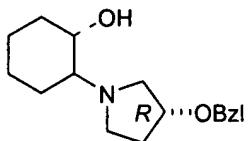
5SSR

141. (New) The compound (5R):



5R

142. (New) The compound (4R):



4R